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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,631	FIGUEIRA ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If tho period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Response to Restriction Requirement, filed July 30, 2004 is acknowledged. Claims 1-27 are pending; claim 27 has been amended. Claims 1-26 are the subject of this Office Action; claim 27 is withdrawn from examiner's consideration as directed to a non-elected invention; see 37 CFR 1.142(b).

DETAILED ACTION

1. Restriciton/Election

Applicant's election with traverse of Group I, claims 1-26 in the reply filed on July 30, 2004 is acknowledged. The traversal is on the ground(s) that because Claim 27 of Group II is directed to the expression vector that is used in the method of Group I both groups should be examined together. In addition, it is Applicants' position that the search and examination of claims 1-27 can be made without serious burden on examiner.

Applicant is reminded that, as indicated in the restriction requirement inventions of Group II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, invention of Group II, the expression vector, can be used for probing with plasmid sequences and not for the method of recombinant synthesis of protein.

If Applicants elected Group I directed to product and the case were allowable, pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims directed to the process of using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are the subject to being rejoined and fully examined for patentability under 37 CFR 1.104. However, the opposite is not the case. Applicants elected the method; in case the method is allowable the claims directed to product cannot be rejoined. Applicants

As to the burden on the examiner, search required for both groups is overlapping but not coextensive as indicated by their different classification and recognized different subject matter. Claims 1-26, drawn to a method of producing a recombinant polypeptide require searching class 345, subclass 69.1, which is not required for claim 27 that requires searching class 435, subclass 320.1. In conclusion, the requirement is still deemed proper and is therefore made FINAL.

1. Objections

The specification is objected to for lack of sequence identification numbers after primer sequences on page 11 [0052].

Claim 1 is objected to for the phrase "a product from metabolic engineering". It seems that Applicants refer to "a product of metabolic engineering".

Claim 14 is objected to for the typographical error in the first line, i.e., "vector1".

Claims 11 and 14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims depend on claim 1 which implicitly includes limitation of claim 11 and 14; otherwise the invention of claim 1 would be inoperative.

2. Rejections

2.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claim 1 is unclear, because it recites the phrase "methylotrophic bacterium under the control of a regulated promoter" which is confusing. This is the production of a recombinant peptide; protein or a product of metabolic engineering that is under control of a regulated promoter, not the bacterium itself.

Part a) of claim 1 is unclear in recitation "a peptide", "a protein", "a product" and "a regulated promoter". These are the peptide, the protein, the product and the regulated promoter that have been already stated in the preamble.

Part c) of claim 1) is confusing because it seems to repeat that what has been said in the preamble. When production of a product is under the control of a regulated promoter that means that expression of the polynucleotide encoding the product is regulated by said promoter. Part c) of the claim is redundant. The claim is examined without part c).

Claim 3 is confusing, because part c) of claim 1 from which claim 3 depends is confusing. If a promoter is regulated by a metal as recited by claim 2, the expression of the protein of interest is regulated by the metal. Applicant is required to cancel claim 3.

Claims 9 and 10 are confusing in recitiation of the phrase "with a component within or from said culture medium". It is not clear whether the product obtained by the method is going to (or reacts) with a component of the medium when said product is still in the medium or after isolation from the medium. In the latter case the reaction is performed in a vessel that does not contain a full medium and microorganism, but only said product and said medium component.

Claims 9 and 10 are indefinite in recitation of the term "biomaterial", which is not defined by the claims or the specification, thus rendering the claims indefinite.

Claim 19-21 are rejected as confusing and broadening the scope of the base claim from which they depend. Claim 19 is directed to a method of claim 1 <u>further</u> comprising controlling the expression of polynucleotides used for production of desired products with a promoter from a gene from an organism other than a methylotrophic bacterium. Applicants invention of claims 1 is directed to the use of a methylotrophic bacterium comprising the expression vector that contains a promoter from another

methylotrophic bacterium. Claims 19-21 broaden the scope of claim 1, because the engineered bacterium either has to comprise an expression vector that contains two promoters or additional expression vector for expression of the same polynucleotide under control of the promoter form an organism other than a methylotrophic bacterium.

For examination purposes it is assumed that the claims are directed to the method of use of a methylotrophic bacterium comprising an expression vector that contains a promoter of a gene from an organism other than a methylotrophic bacterium.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 and dependent claims 2-18 and 22-26 are directed to a genus of methods that are not sufficiently described in the disclosure. The methods use a large and variable genus of methylotrophic (faculatative and obligate methylotrophs) bacteria, transformed with a large and versatile genus of plasmids comprising any regulated promoter or a metal regulated promoters wherein said promoter originates from any methylotrophic bacterium. The specification does not provide sufficient description of the genus of transformed bacteria. Applicants teach two transformants of *Methylobacterium extorquens* that comprise plasmids p*mmoX*-GFP-pRK310 and p*mmoX*-GFP-pVK101 containing promoter of *mmoX* gene from *Methylosinus trichosporium* OB3b, wherein the expression of the plasmid is regulated by Cu^{2+} ions. The transformants of *Methylobacterium extorquens* containing plasmids p*mmoX*-GFP-pRK310 and p*mmoX*-GFP-pVK101 do not provide identifying characteristics of all transformants of methylotrophic bacteria that are transformed with plasmid containing any regulated promoter from any methylotrophic bacteria. Thus, one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

Claim 2 and 3 are directed to the method of claim 1 wherein the regulated promoter is a metal regulated promoter. The claims are directed to a large and versatile genus of methods of using a genus of methylotroph bacterium transformed with a plasmid comprising any metal regulated promoter from methylorphic microorganisms The specification teaches only one representative of the genus of promoters, which is the promoter of *mmX* gene from *Methylosinus trichosporium* OB3b regulated by Cu2+

ions. Applicants fail to disclose the use of any other promoter that is regulated by any other metal ions. Thus, one skilled in the art is not convinced that the Applicants had the possession of the claimed invention at the time of filling of the application.

Furthermore, claims 9 and 10 are rejected for a complete lack of written description of a biomaterial which is going to be produced in result of the reaction of the product of method of claim 1 with the medium component or medium component, during fermentation or thereafter. In addition, claims 9 and 10 are rejected for a complete lack of written description of the medium component, with which the product of claim 1 is going to react during fermentation or thereafter. One skilled in the art is not convinced that the Applicants had the possession of the claimed invention at the time of filling of the application.

Claim 19 is rejected as directed to the method of use of a methylotrophic bacterium transformed with a plasmid comprising a regulated promoter from any gene from any organism other than a methylotrophic bacterium. The claim is directed to a large genus of methods, wherein the methods use a large and versatile genus of plasmids comprising any possible gene promoter from any organism other than a methylotrophic bacterium. The specification fails to sufficiently describe the genus of plasmids, because the specification provides only two plasmids, p*Lac*-GFP-pJB3KmD and p*Lac*-GFP-pRK310 that comprise lacZ promoter of E.coli. One skilled in the art realizes that neither plasmid p*Lac*-GFP-pJB3KmD nor p*Lac*-GFP-pRK310 provide an identifying characteristics of the genus of plasmids comprising any regulated promoter from any possible gene from any organism other than a methylotrophic bacterium.

Thus, one skilled in the art is not convinced that Applicants had the possession of the claimed invention at the time the Application was filed.

Claim 17, 18, 20 and 21 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is lacking the description of biologic deposit. The invention appears to employ novel plasmids: p*mmoX*-GFP-pRK310, p*mmoX*-GFP-pVK101, p*Lac*-GFP-pJB3KmD and p*Lac*-GFP-pRK310. Since the plasmids are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The sequence of claimed plasmid is not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirement of 35 U.S.C. § 112 may be satisfied by deposit of the plasmids or transformed methylotrophic bacteria. The specification does not disclose a repeatable process to obtain the plasmid and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of the plasmid should have been made in accordance with 37 C.F.R. § 1.801-1.809.

If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicant, or a statement by an attorney of record over his/her signature and registration number, stating that the specific microorganism has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to

certify that the deposit meets the criteria set forth in 37 C.F.R. § 1.801-1.809, the applicant may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his/her signature and registration number, showing that:

(1) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(2) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;

(3) the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

(4) the deposit will be replaced if it should ever become inviable.

3.2.2. Lack of enablement

Improper incorporation by reference

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Applicants refer the one skilled in the art to many publications that are crucial to make the claimed invention, particularly to make plasmids p*mmoX*-GFP-pRK310, p*mmoX*-GFP-pVK101, p*Lac*-GFP-pJB3KmD and p*Lac*-GFP-pRK310; page

13, under the Table. However, the attempt to incorporate subject matter of these publications into this application is improper because the plasmids are essential to the instant invention. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing publication. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

3.3. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-6, 11, 14, 16, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toyoma et al. (Construction of insertion and deletion mxa mutants of *Methylobacterium extorquens* AM1 by electroporation, FEMS Microbiology Letters, 1998, 166, 1-7) as applied the claims above, and further in view of Nielsen, et al. (Cooper-dependent reciprocal transcriptional regulation of methane monoxygenase

genes in *Methylococcus capsulates* and *Methylosinus trichosporium*, Molecular Microbiology, 1997, 25, 399-409) and Alper (Engineering Metabolism for Commercial Gains, Science, 1999, 283, 1625-1626).

The claims are directed to a method of obtaining and use of large and variable genus of methylotrophic (faculatative and obligate methylotrophs) bacteria, transformed with a large and versatile genus of plasmids comprising any regulated promoter or a metal regulated promoter wherein said promoter originates from any methylotrophic bacterium.

Toyoma at al. teach plasmid pHT9 (Table 1, page 3) that comprises mxaFJGIR fragment of the mxaFJGIR(S)ACKLD operon of methanol dehydrogenase under control of mxaF gene promoter which is a promoter from a methylotrophic bacterium, *Methylobacterium extorquens* AM1. Toyoma et al also teach producing, by electroporation (page 3, line 3, left column under Table 1) of transformants of *Methylobacterium extorquens* AM1 with plasmid pHT9. Toyoma uses the transformants to expresss the mxaFJGIR polypeptide for complementation of the mutants of the genes of mxa operon; see table 12, page 4. Toyoma et al, however do not teach how or whether the mxaF promoter is regulated.

Nielsen et al. teach mmoX promoter from Methylosinus trichosporium that is controlled by concentration of Cu2+ ion in the medium. Nielsen et al also teach pMTL1000 plasmid that contains nucleotides 1-6044 of smmo gene (including the Cu2+ regulated promoter) of Methylosinus trichosporium OB3b, see Table 1, page 401.

Alper reviews current advances in engineering metabolism for commercial gains and particularly points to works by Lindstrom and her co-workers who have created an efficient vector system for introducing new genes into Methylobacterium that can grow on one carbon sources such as methanol. Alper emphasizes "Because methanol is easy to make from methane, found in natural gas, genetically engineered Methylobacterium could replace some of the existing chemical processes for turning this readily available feedstock into the dozens of commodity chemicals that go into the manufacture of almost every polymer now in use", see page 3, the second paragraph, of the web site printout.

It would have been obvious for that of ordinary skills in the art to introduce into *Methylobacterium extorquens* an expression vector as Toyoma did, wherein said expression vector had been modified by replacing the mxaFJGIR fragment of the mxaFJGIR(S)ACKLD operon of *Methylobacterium extorquens M1* with the a metal controlled mmoX promoter operably linked to any polypeptide, as taught by Nielsen et al. and further use such metabolically engineered methylotrophic bacterium for production of polypeptides and/or other products of metabolic engineering for commercial purposes as taught by Alper. The motivation was provided by Alper, as quoted above, and the probability of success was very high, because Toyama proved that *Methylobacterium extorquens* transformed with an expression vector under control of a methylotrophic promoter can successfully produce a protein. Thus, the claimed

invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

4. Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0937. The fax phone number for this Group is (703) 872-9306.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

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